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Brief Research Communication

Linkage Study Between Manic-Depressive Illness and Chromosome 21

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Chromosome 21, of interest as potentially containing a disease gene for manic-depressive illness as possible evidence for a gene predisposing to affective disorder, has recently been reported in a single large family as well as samples of families.

The present study investigates for linkage between manic-depressive illness and markers covering the long arm of chromosome 21 in two manic-depressive families, using ten microsatellite polymorphisms as markers.

No conclusive evidence for a disease gene on the long arm of chromosome 21 was found. Assuming either a dominant or recessive mode of inheritance, close linkage to the marker PFKL, which has been reported as possibly linked to affective disorder, seems unlikely in the families studied here. PFKL and more telomeric markers yielded small positive lod scores at higher recombination fractions in the largest family, and small positive lod scores at lower recombination fractions in the affecteds-only analyses in the smallest family.

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KEY WORDS: affective disorder, linkage analyses, PFKL

INTRODUCTION

Chromosome 21 is of interest as potentially containing a disease gene for manic-depressive illness. In large samples of families with affective disorder, Straub et al. [1994] and Gurling et al. [1995] found possible evidence for a disease gene on chromosome 21.

Mania seems to be less common in patients with trisomy 21, and this might imply that a dominant or recessive disease gene for manic-depressive illness is located on chromosome 21, as suggested by Craddock and Owen [1994]. The critical region for developing Down's syndrome involves at least part of 21q22.3 [Delabar et al., 1993], the same region for which linkage has been reported in a single large family [Straub et al., 1994].

Finally, a deletion of the short arm of chromosome 21 in a mother and child who both had bipolar affective disorder has been reported [El-Badramany et al., 1989]. The clinical significance of a deletion of 21p is, however, uncertain [El-Badramany et al., 1989].

The present study reports linkage analyses between manic-depressive illness and markers from chromosome 21 in two manic-depressive families, using ten microsatellite polymorphisms as markers. Two large families were identified through bipolar probands in contact with the Psychiatric Hospital in Aarhus, Denmark (Fig. 1). Sex and birth order have been concealed to ensure confidentiality. Diagnostic information was obtained by interview of family members by H.Ew. and O.M. using the semistructured interview "Present State Examination," 10th edition [Wing et al., 1990], and information from relatives, hospital records, and general practitioners. A report was written on the basis of the above-mentioned sources. The reports and the medical records were reviewed by a senior psychiatrist experienced in ICD-10, Dr. A. Bertelsen, without access to the family data or laboratory results, and his diagnoses, made in accordance with ICD-10, Diagnostic Criteria for Research, were recorded. No one in the blood line was diagnosed as having schizophrenia, schizoaffective disorder, or any other type of psychosis other than manic-depressive illness.

Further details of the study concerning exclusion criteria, interrater reliability and diagnoses according to RDC have been reported earlier [Ewald et al., 1994a,b].

The following markers were chosen: D21S215 at 21q11.2, D21S214 and D21S210 at 21q21.2, GART at

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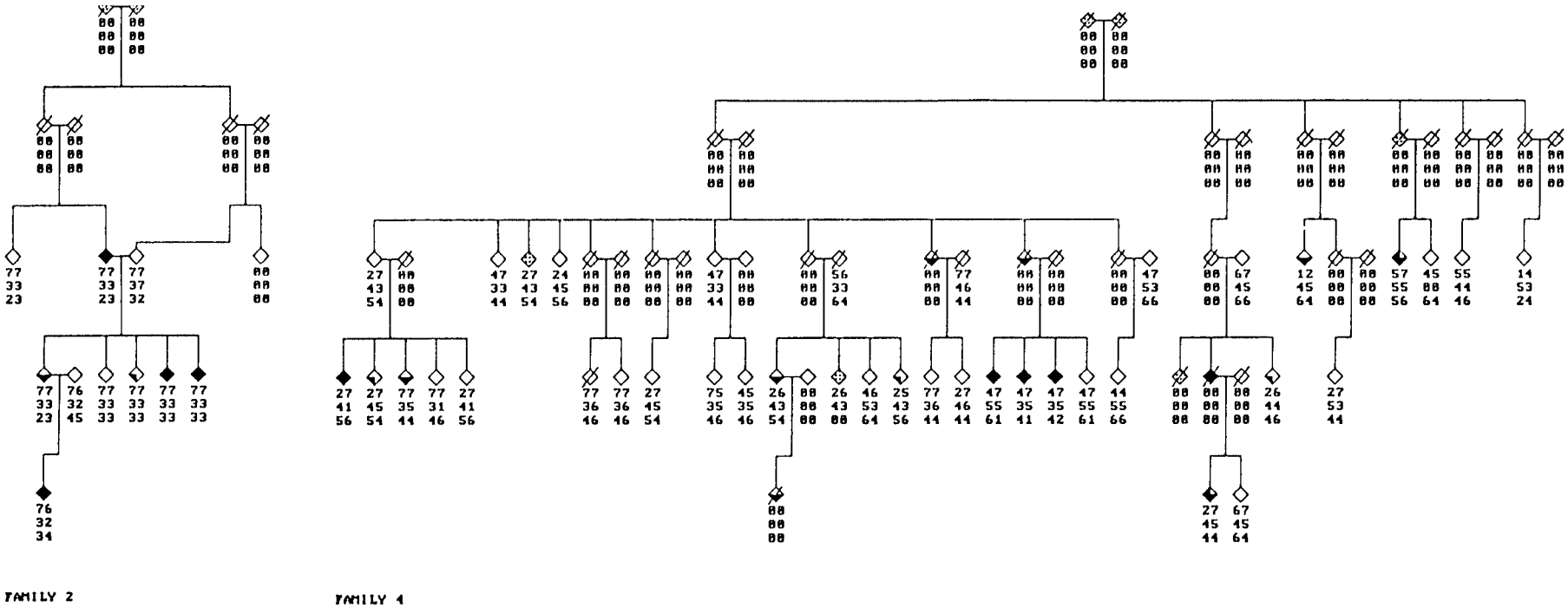

Fig. 1. The two pedigrees examined for linkage between manic-depressive illness and markers on chromosome 21. In family 2, the fourth symbol in generation three refers to 10 unaffected siblings aged 60 years or more. Alleles for marker PFKL are above, D21S171 alleles are in the middle, and D21S1575 alleles are at the bottom. ◆, Bipolar affective disorder with mania or mania single episode. ⬖, Hypomania and moderate severe depressive episode (s). ⬙, Two or more depressive episodes of at least moderate severity. ⬖, Only one depressive episode of moderate severity or recurrent minor depression. ⬖, Persons who presently have unknown phenotype.

21q22.1, and D21S156, HMG14, D21S212, PFKL, D21S171 and D21S1575 [Blouin, 1994] at 21q22.3. Approximate distances between markers have been reported [NIH/CEPH Collaborative Mapping Group, 1992; Lawrence et al., 1993; Delabar et al., 1993] and are shown in Figure 2. Some maps place PFKL distal to D21S171 [Delabar et al., 1993], and the distance from PFKL to the telomere has been estimated to only 1 Mb [Lawrence et al., 1993]. D15S1575 is located distal to PFKL. DNA was extracted by standard techniques. Primers for D21S215, D21S214, D21S210, GART, HMG14 and PFKL were kindly provided by the Nordic Microsatellite consortium in Uppsala. These microsatellites, D21S212 and D21S1575, were genotyped as described earlier by Eiberg et al. [1994].

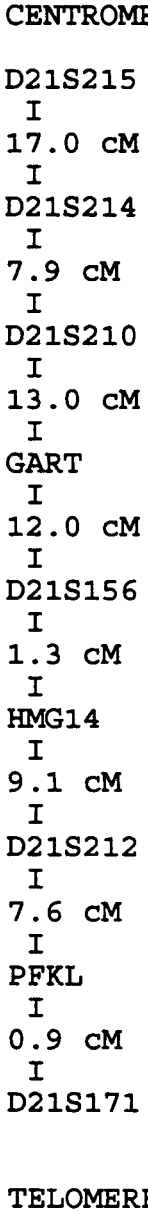

Fig. 2. The DNA markers from chromosome 21 investigated in the present study and the approximate distances between them in centi-Morgans. D21S1575 is located telomeric to D21S171.

Primers for D21S156 and D21S171 were obtained through our collaborators from the European Science Foundation programme on the Molecular Neurobiology of Mental Illness. These markers were typed using a silver staining method [Ewald et al., 1994a]. The gels were analyzed by two independent observers without access to the clinical data.

In family 4, two unaffected individuals were coded genotype unknown for marker D21S215, four unaffected individuals were coded genotype unknown for D21S210, one unaffected person, 28 in generation III, was untyped for D21S156 and D21S171, and one person with unknown phenotype was coded genotype unknown for D21S1575. Approximately 60 persons were routinely genotyped.

Lod scores were calculated using the computer program LINKAGE [Lathrop et al., 1984]. Three different phenotypic models assuming a dominant mode of transmission and one recessive model were used in the analyses (Table I). Model 1 included 11 affected individuals, model 2 and the recessive model included 18 affected individuals and model 3 included 22 affected individuals. Individuals with affective disorders other than those included by the model in question were scored as phenotype unknown when analysing that model [Ott, 1990].

Conservative values of 0.60, 0.65, 0.70 and 0.60 for maximum penetrance were chosen for dominant models 1–3 and the recessive model, respectively. The penetrances for persons homozygous for the normal allele were set relatively high and age-dependent, adding up to 0.005, 0.02, 0.06 and 0.02 for dominant models 1–3 and the recessive model, respectively. The exact age-dependent penetrances for the different models have been reported earlier [Ewald et al., 1994a, b]. The frequency of the disease allele was set to 0.004 for model 1, to 0.01 for models 2 and 3, and to 0.1 for the recessive model. We also performed an affecteds-only analysis for all models [Ott, 1990; Edwards, 1982], using the same penetrance ratios for the affected as in the models mentioned above.

Simulations were done using SLINK [Ott, 1989; Weeks et al., 1990] to investigate if family 4 alone was sufficient to detect linkage, given the diagnostic models and genetic parameters used, and using SIMULATE [Ott and Terwilliger, 1992] to estimate the risk of obtaining positive lod scores with an unlinked marker. For both analyses, 1,000 replicates of the large family were simulated for a marker with six equally frequent alleles as this reflects the heterozygosity of several recently available markers.

Frequencies for the microsatellite marker alleles were calculated from individuals who married into the families (Ott, 1992), including three individuals from family 4, who are presently excluded from the linkage analysis.

For dominant models, results from the two-point analyses and markers from chromosome 21 are shown in Table I. PFKL was not informative in family 2 (Fig. 1) and is thus only mentioned for family 4. No evidence

TABLE I. Lod Scores Assuming a Dominant Mode of Transmission, With Results From the Affecteds-Only Analyses in Parentheses

	Recombination fraction			
	0.00	0.05	0.10	0.20
Model 1[a]				
Family 4				
D21S215	−1.96 (−2.16)	−1.01 (−0.98)	−0.62 (−0.59)	−0.24 (−0.23)
D21S214	−2.19 (−2.64)	−1.36 (−1.68)	−1.01 (−1.17)	−0.56 (−0.63)
D21S210	−0.84 (−0.38)	−0.13 (0.13)	0.07 (0.27)	0.20 (0.32)
GART	−2.50 (−1.96)	−1.36 (−0.99)	−0.99 (−0.56)	−0.58 (−0.14)
HMG14	−0.22 (0.15)	−0.22 (0.09)	−0.19 (0.06)	−0.07 (0.06)
D21S156	−1.17 (−1.92)	−0.97 (−0.72)	−0.75 (−0.37)	−0.37 (−0.08)
D21S212	−2.36 (−2.59)	−1.34 (−0.95)	−0.79 (−0.39)	−0.19 (0.01)
PFKL	−1.39 (−1.14)	−0.51 (−0.27)	−0.14 (0.04)	0.16 (0.25)
D21S171	−1.05 (−1.69)	−0.93 (−1.17)	−0.75 (−0.74)	−0.35 (−0.27)
D21S1575	−2.83 (−1.68)	−0.79 (−0.77)	−0.16 (−0.29)	0.26 (0.12)
Both families				
D21S215	−1.91 (−2.10)	−0.97 (−0.93)	−0.59 (−0.55)	−0.22 (−0.21)
D21S214	−3.40 (−3.84)	−2.52 (−2.42)	−1.93 (−1.70)	−1.08 (−0.93)
D21S210	−3.14 (−0.82)	−1.59 (−0.29)	−0.95 (−0.11)	−0.34 (0.05)
GART	−5.43 (−3.60)	−2.88 (−1.94)	−2.02 (−1.22)	−1.13 (−0.50)
HMG14	−1.54 (−0.03)	−1.46 (−0.15)	−1.22 (−0.19)	−0.68 (−0.17)
D21S156	−3.25 (−1.68)	−2.44 (−0.59)	−1.77 (−0.33)	−0.90 (−0.14)
D21S212	−3.78 (−2.54)	−2.66 (−1.00)	−1.89 (−0.51)	−0.84 (−0.15)
D21S171	−1.20 (−1.59)	−1.05 (−1.09)	−0.84 (−0.68)	−0.40 (−0.24)
D21S1575	−2.85 (−1.09)	−0.77 (−0.27)	−0.13 (0.13)	0.27 (0.37)
Model 2[b]				
Family 4				
D21S215	−3.75 (−1.43)	−2.24 (−0.91)	−1.53 (−0.68)	−0.75 (−0.38)
D21S214	−3.90 (−2.20)	−2.69 (−1.60)	−1.92 (−1.21)	−0.97 (−0.67)
D21S210	−0.98 (−0.20)	−0.30 (−0.04)	−0.03 (0.08)	0.19 (0.18)
GART	−3.99 (−1.62)	−2.45 (−0.79)	−1.66 (−0.40)	−0.76 (−0.05)
HMG14	−0.16 (0.11)	−0.16 (0.09)	−0.14 (0.08)	−0.05 (0.08)
D21S156	−3.77 (−1.94)	−1.97 (−0.83)	−1.23 (−0.43)	−0.48 (−0.07)
D21S212	−4.04 (−2.84)	−1.77 (−1.40)	−0.91 (−0.76)	−0.10 (−0.20)
PFKL	−2.11 (−0.45)	−0.41 (0.12)	0.11 (0.36)	0.46 (0.45)
D21S171	−3.49 (−1.75)	−1.45 (−0.92)	−0.70 (−0.50)	−0.06 (−0.12)
D21S1575	−3.79 (−1.26)	−1.12 (−0.70)	−0.36 (−0.41)	0.21 (−0.05)
Both families				
D21S215	−3.70 (−1.37)	−2.19 (−0.86)	−1.50 (−0.64)	−0.73 (−0.36)
D21S214	−6.15 (−3.34)	−4.19 (−2.31)	−2.97 (−1.72)	−1.52 (−0.96)
D21S210	−3.34 (−0.61)	−1.74 (−0.43)	−1.03 (−0.27)	−0.34 (−0.07)
GART	−6.68 (−2.88)	−3.93 (−1.63)	−2.69 (−1.01)	−1.31 (−0.38)
HMG14	−2.34 (−0.10)	−1.80 (−0.18)	−1.33 (−0.20)	−0.69 (−0.15)
D21S156	−5.99 (−1.70)	−3.44 (−0.70)	−2.25 (−0.38)	−1.01 (−0.12)
D21S212	−6.24 (−2.81)	−3.49 (−1.47)	−2.17 (−0.89)	−0.78 (−0.37)
D21S171	−3.65 (−1.65)	−1.58 (−0.84)	−0.80 (−0.44)	−0.11 (−0.09)
D21S1575	−3.83 (−0.69)	−1.12 (−0.21)	−0.34 (−0.01)	0.22 (0.19)
Model 3[c]				
Family 4				
D21S215	−3.74 (−1.18)	−2.28 (−0.69)	−1.59 (−0.50)	−0.80 (−0.29)
D21S214	−3.85 (−2.04)	−2.68 (−1.51)	−1.92 (−1.14)	−0.97 (−0.63)
D21S210	−1.38 (−0.11)	−0.66 (−0.06)	−0.35 (−0.02)	−0.04 (0.06)
GART	−4.27 (−1.82)	−2.57 (−0.89)	−1.75 (−0.47)	−0.81 (−0.07)
HMG14	−0.16 (0.16)	−0.16 (0.13)	−0.14 (0.12)	−0.06 (0.10)
D21S156	−3.84 (−1.78)	−1.98 (−0.62)	−1.24 (−0.25)	−0.48 (0.02)
D21S212	−4.26 (−2.85)	−1.76 (−1.29)	−0.88 (−0.67)	−0.06 (−0.14)
PFKL	−1.97 (−0.06)	−0.15 (0.46)	0.36 (0.65)	0.66 (0.65)
D21S171	−3.24 (−1.40)	−1.16 (−0.62)	−0.43 (−0.24)	0.14 (0.06)
D21S1575	−3.68 (−0.90)	−0.71 (−0.41)	−0.00 (−0.17)	0.47 (0.10)
Both families				
D21S215	−3.68 (−1.11)	−2.23 (−0.63)	−1.55 (−0.46)	−0.77 (−0.27)
D21S214	−6.21 (−3.07)	−4.22 (−2.14)	−3.00 (−1.59)	−1.55 (−0.88)
D21S210	−3.75 (−0.54)	−1.98 (−0.45)	−1.25 (−0.35)	−0.51 (−0.16)
GART	−7.17 (−2.97)	−4.25 (−1.67)	−2.93 (−1.05)	−1.45 (−0.40)
HMG14	−2.18 (0.06)	−1.69 (−0.03)	−1.24 (−0.06)	−0.66 (−0.06)
D21S156	−6.18 (−1.43)	−3.65 (−0.38)	−2.43 (−0.11)	−1.11 (0.02)
D21S212	−6.35 (−2.71)	−3.38 (−1.25)	−2.07 (−0.70)	−0.71 (−0.23)
D21S171	−3.42 (−1.29)	−1.30 (−0.53)	−0.53 (−0.17)	0.08 (0.09)
D21S1575	−3.59 (−0.21)	−0.59 (0.19)	0.13 (0.43)	0.56 (0.41)

[a]Model 1: Includes as affected individuals diagnosed as bipolar affective disorder or single episode mania (one person). We restricted the criteria for bipolar disorder by excluding individuals with only mild episodes (hypomania and mild depression). [b]Model 2: As model 1 and including individuals with at least two depressive episodes of at least moderate severity. [c]Model 3: As model 2 and including individuals with at least one episode of at least moderate severity or recurrent mild depression.

of linkage was found between manic-depressive illness and any of the markers.

In family 4, dominant models 1,2 and 3 yielded low positive lod scores for PFKL, peaking at a recombination fraction of 0.20 or 0.30. The affecteds-only analyses showed that these lod scores were mainly or only derived from affected individuals. Flanking markers, D21S171, and D21S212, yielded mostly negative lod scores, though low positive lod scores were obtained at higher recombination fractions in some of the models. D21S1575, which is located distal to PFKL and D21S171, probably within less than one Megabase [Blouin, 1994; Lawrence et al., 1993], yielded low positive lod scores at higher recombination fractions in family 4, while it was relatively uninformative in family 2.

Assuming a recessive mode of inheritance and homogeneity, low positive lod scores were obtained for the marker D21S156, also in the affecteds-only analyses (peaking with a lod score of 0.74 at a recombination fraction of 0.05). These were the highest two-point lod scores found in the present study. This was, however, not supported by the closely linked marker HMG14 or nearby marker D21S212. Low positive lod scores were found for D21S1575 in family 2 for all models, with a lod score of 0.69 at zero recombination fraction for model 3 being the highest.

Neither PFKL nor D21S171 was fully informative (Fig. 1) in the two-point analyses. The two markers were linked with a maximum lod score of 9.02 at zero recombination fraction in family 4, i.e., no recombinants were observed. To increase the amount of information in family 4, these markers were considered as one locus and analysed with LINKMAP (OS/2 version 5.20) with a sex-averaged distance between markers of 0.00 (Table II). For model 1, the lod score at PFKL/D21S171 dropped to −1.80 and for models 2, 3 and the recessive model, the lod scores at PFKL/D21S171 were below −2. For all dominant models, positive lod scores were obtained at higher recombination fractions, especially in the affecteds-only analyses.

The simulations using SLINK showed reasonable power for the dominant models in family 4 (Table III). The simulations with SIMULATE (Table III) showed that in family 4, lod scores above 1 occur relatively rarely with an unlinked marker. In general, two-point analyses confirmed linkage between adjacent markers at appropriate distances.

In one out of 47 families with affective disorder, Straub et al. [1994] found a lod score of 3.41 at zero recombination fraction for the marker PFKL at 21q22.3. Dominant mode of inheritance, a phenotypic model similar to our model 2, and affecteds-only analysis were applied. Several other markers at 21q22.3 yielded positive lod scores, including D21S156, HMG14, D21S212 and D21S171, assuming a dominant and/or recessive mode of inheritance. In a few of the 46 other families, low positive lod scores were found for PFKL and D21S171, at lower recombination fractions, while multipoint analyses yielded highly negative lod scores at low recombination fractions but a maximum lod score of 2.80 at a distance of about 30 cM. While heterogeneity testing for PFKL weakened the evidence for linkage, the affected pedigree member method [Weeks and Lange, 1988], combining all 47 families, yielded very low *P*-values for PFKL. The PFKL gene itself is encoding a liver enzyme, phosphofructokinase, which is of no obvious significance for the pathophysiology of manic-depressive illness. The exact location of the putative locus is unclear [Straub et al., 1994], and apparently no attempt was made to estimate the mode of inheritance by maximising lod scores [Greenberg and Berger, 1994; Hodge and Elston, 1994]. The evidence for a possible necessary or susceptibility disease gene [Greenberg, 1993] on chromosome 21q has not yet been replicated, and this may be difficult even if such a gene exists [Suarez et al., 1994].

Assuming a dominant mode of inheritance, Pakstis et al. [1991] investigated two markers on chromosome 21q, D21S11 at 21q21 and D21S1 at 21q11.2-q21, in an extended pedigree from the Old Order Amish (OOA 110) without finding evidence of linkage. Ginns et al. [1992] reported that five markers from chromosome 21 had been tested in a larger extension of the same pedigree (OOA 110) without finding evidence of linkage. Assuming homogeneity in 19 families and a dominant mode of inheritance, Gejman et al. [1993] excluded linkage to two markers at 21q11.2 and D21S156 and D21S168 at 21q22.3. Coon et al. [1993] tested seven markers on chromosome 21, assuming homogeneity in eight families and dominant mode of inheritance. Close linkage to four of these markers were excluded.

The present study did not find evidence of close linkage between manic-depressive illness and markers from the long arm of chromosome 21. For dominant

TABLE II. Lod scores With PFKL and D21S171 Considered as One Locus in Family 4, With Results From the Affecteds-Only Analyses Mentioned in Parentheses

	Recombination fraction				
	0.00	0.05	0.10	0.20	0.30
Model 1					
PFKL/D21S171	−1.80 (−1.29)	−0.61 (−0.54)	−0.28 (−0.11)	0.16 (0.27)	0.32 (0.33)
Model 2					
PFKL/D21S171	−2.42 (−1.00)	−0.30 (−0.06)	0.38 (0.33)	0.80 (0.57)	0.32 (0.47)
Model 3					
PFKL/D21S171	−2.13 (−0.56)	−0.01 (0.30)	0.65 (0.64)	0.99 (0.79)	0.71 (0.61)
Recessive model					
PFKL/D21S171	−2.59 (−0.92)	−1.09 (−0.46)	−0.58 (−0.22)	−0.02 (0.00)	−0.02 (0.04)

TABLE III. Results From Two-Point Simulation Analyses in Family 4*

	ELOD	Min.	Max.	% lod scores (Z max.) larger than >1.0	>2.0	>3.0
Dominant model 1						
Linked marker	1.59	−1.75	4.67	70.3	40.8	14.2
Unlinked marker	−1.23	−3.16	2.00	1.8	0.1	0.0
Dominant model 2						
Linked marker	2.35	−2.56	5.80	85.2	59.6	34.2
Unlinked marker	−2.42	−5.35	2.40	1.9	0.1	0.0
Dominant model 3						
Linked marker	2.50	−2.79	6.02	86.9	63.0	37.9
Unlinked marker	−2.49	−5.41	2.74	1.5	0.2	0.0
Recessive model						
Linked marker	0.98	−1.84	3.42	49.9	10.9	0.7
Unlinked marker	−1.08	−3.52	1.95	1.0	0.0	0.0

*Results from SLINK (marker linked at theta = 0.01) and SIMULATE (marker unlinked). Based on 1,000 replicates and six marker alleles of equal frequency. The average maximum lod score (ELOD), minimum and maximum values are at theta = 0.01 for SLINK and 0.00 for SIMULATE.

models 2 and 3, lod scores below −2 were found close to markers D21S156, PFKL, D21S171, and D21S1575, assuming homogeneity and also in family 4 alone when the phenotypes of all family members were included in the analyses, except that for model 3 in family 4, PFKL was −1.97. Close linkage to D21S212 was excluded for all models in family 4 alone and assuming homogeneity.

In family 4, assuming a dominant mode of inheritance, low positive lod scores were observed at some distance from PFKL and D21S1575 in the two-point analyses, also when PFKL and D21S171 were considered as one locus. This is not strong evidence for a major gene as there was no indication of linkage for the more proximal markers tested, and the distance from D21S1575 to the telomere has been estimated to only 100 kilobases [Blouin, 1994]. Simulations with a highly informative unlinked marker showed that lod scores around 1 were not very rare. Furthermore, the lod scores for narrower phenotypic models and inspection of the most likely haplotypes in family 4 shows that a few persons with bipolar affective disorder and recurrent depression, the putative core phenotypes of affective disorder, were counted as recombinants. In our opinion this further weakens the evidence for a major gene in this region.

However, it is interesting that Straub et al. [1994] and Gurling et al. [1995] also found positive lod scores at a higher recombination fraction in their collections of families in the multipoint analyses with PFKL and D21S171. An alternative explanation is that there might be misspecification of the phenotypic model and/or the genetic parameters and that a perhaps weaker gene predisposing to manic-depressive illness is present on chromosome 21q. The use of wrong estimates for genetic parameters leads to more bias of the recombination fraction than of the lod score [Clerget-Darpoux et al., 1986], probably also if the true mode of inheritance is oligogenic [Vieland et al., 1992]. Detection of susceptibility genes in pedigrees may require testing of a very large collection of families [Greenberg, 1993] and a large sample of markers, and should perhaps await develop ment of more appropriate methods [Babron et al., 1993]. Furthermore, a truly systematic genome wide screen for necessary disease genes with very informative markers has yet to be reported, as well in sufficient large families as in large collections of smaller families [Greenberg, 1992], and possible evidence for both necessary and susceptibility genes thus has to be interpreted with caution.

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